Absence of CCL2 is sufficient to restore hippocampal neurogenesis following cranial irradiation.

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Public Summary:
Some childhood brain tumors can be cured with aggressive cancer therapy but children who receive cranial radiation as part of their treatment often suffer a progressive and debilitating decline in cognitive function. Our earlier work showed that radiation therapy ablates stem cells in the brain and prevents ongoing brain development that normally occurs in early childhood. Those few stem cells that remain become dysfunctional, in part due to a permanent tissue inflammation caused by radiation injury. In this report, we discovered that genetic deletion of a single immune signaling molecule in mice reduced inflammation and allowed the remaining neural stem cells to recover their normal function and resume neurogenesis. These results suggest that modifying inflammation in the brain following therapy may reduce or even prevent the cognitive decline that plagues otherwise successful treatment of childhood cancers.

Scientific Abstract:
Cranial irradiation for the treatment of brain tumors causes a delayed and progressive cognitive decline that is pronounced in young patients. Dysregulation of neural stem and progenitor cells is thought to contribute to these effects by altering early childhood brain development. Earlier work has shown that irradiation creates a chronic neuroinflammatory state that severely and selectively impairs postnatal and adult neurogenesis. Here we show that irradiation induces a transient non-classical cytokine response with selective upregulation of CCL2/monocyte chemoattractant protein-1 (MCP-1). Absence of CCL2 signaling in the hours after irradiation is alone sufficient to attenuate chronic microglia activation and allow the recovery of neurogenesis in the weeks following irradiation. This identifies CCL2 signaling as a potential clinical target for moderating the long-term defects in neural stem cell function following cranial radiation in children.